REMARKS

Claims 1-32 are pending in this application. Claims 5, 6, 15 and 32 have been withdrawn as being directed to a non-elected species. Claims 1-4, 7-8, 10-14, 16-26 and 31 have been amended.

Claims 5, 6, 15 and 32 have been withdrawn from consideration as being directed to a non-elected species. Applicant notes that upon allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR § 1.141.

Claims 1-4, 7-8, 10-14, 16-26 and 31 have been amended, for the sole reason of advancing prosecution. Applicant, by canceling or amending any claims herein, makes no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicant reserves the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Claim 1 has been amended to recite "[a]n assay for determining the concentration of rapamycin or a rapamycin analog in a sample, the rapamycin or rapamycin analog being capable of binding to FKBP12 protein or a binding domain thereof, the assay comprising: (i) contacting the sample with FKBP12 protein, or with a rapamycin binding fragment of the FKBP12 protein that maintains the rapamycin binding properties, for a time period and under conditions allowing formation of rapamycin/FKBP12 complex; (ii) contacting the rapamycin/FKBP12 complex with a complex-binding domain of mTOR for a time period and under

conditions enabling binding of the complex to the complex-binding domain; (iii) detecting the amounts of said complex-binding domain that is bound to the rapamycin/FKBP12 complex; (iv) comparing the amounts detected in (iii) to a calibration curve, thereby determining the concentration of the rampamycin in the sample." Support for claim 1, as amended, can be found throughout the specification and claims as originally filed.

Claims 2-4, 7-14 and 17-19 and depend, either directly or indirectly, from claim 1. Claims 2-4, 7-8, 10-14 and 17-19 have been amended to be in a form consistent with U.S. practice.

Claim 20 has been amended to recite "[a] kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample, the kit comprising: a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate; and a complex-binding domain of mTOR linked to a label that may be detected or that may generate a signal." Support for claim 20, as amended, can be found throughout the specification and claims as originally filed.

Claims 20-26 and 31 depend, either directly or indirectly, from claim 20. Claims 20-26 and 31 have been amended to be in a form consistent with U.S. practice.

No new matter has been added.

The specification has been amended to expressly indicate that the present application is a National Phase Application filed under 35 U.S.C. 371 as a national stage of PCT/IL2004/001172, with the filing date of December 29, 2004, an application claiming the benefit under 35 USC 119(e) U.S. Provisional Patent

Application No. 60/532,552, filed on December 29, 2003. Additionally, the specification has been amended to properly describe trademarked goods and services. Specifically, the terms SEPHAROSE®, TALON® and CLONTECH® now appear in capital letters, accompanied by generic descriptions.

No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. At page 3 of the Official Action, the Examiner requests that Applicant insert the claim to priority made in the originally filed application, and acknowledged in the Official Filing receipt.

Applicant thanks the Examiner for the request to amend the specification to include an indication that the present application is a National Phase Application filed under 35 U.S.C. 371 as a national stage of PCT/IL2004/001172, with the filing date of December 29, 2004, an application claiming the benefit under 35 USC 119(e) U.S. Provisional Patent Application No. 60/532,552, filed on December 29, 2003. Applicant respectfully submits that the priority information was listed in the coversheet of the originally filed application and on the Inventor's Declaration. Pursuant thereto, Applicant submits that the priority information was also listed on the Official Filing Receipt. Accordingly, Applicant submits that the priority information is now properly cross-referenced in the specification.

II. At page 5 of the Official Action, the specification is objected to as not properly describing trademarked goods and services.

The Examiner requests that Applicant provide generic terminology for trademarked goods and services disclosed in the present specification. Additionally, the Examiner requests that Applicant capitalize the text of the trademarks.

In view of the remarks set forth herein, this objection is respectfully traversed.

As discussed, the specification has been amended to properly describe trademarked goods and services. Specifically, the terms SEPHAROSE®, TALON® and CLONTECH® now appear in capital letters, accompanied by generic descriptions.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, Applicant submits that the specification is compliant with the Examiner's request. Accordingly, the Examiner is respectfully requested to withdraw this objection.

III. At page 3 of the Official Action, claims 1-4, 7-9, 13-17 and 20-25 have been rejected under 35 USC § 103(a) as obvious over MacFarlane et al. (US Patent No. 5,650,288) in view of Chen et al. (US Patent No. 4,385,126) and Clakson et al. (US Patent No. 6,187,757).

The Examiner asserts that it would have been obvious to utilize a sandwich assay method of Chen et al. in the method of assaying a blood sample for rampamycin, as allegedly taught by MacFarlane, in order to perform an assay to detect the concentration of rampamycin using FKBP12 and mTOR of Clakson et al.

In view of the remarks set forth herein, this rejection is respectfully traversed because a prima facie case of obviousness has not been established.

To establish a *prima facie* case of obviousness, the Examiner must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. 398 at 417.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

It is submitted that a *prima facie* case of obviousness has not been established because nothing in the applied references, whether taken alone or in combination teach or suggest all of the elements of the present claims, as required by *In re Wilson*.

Independent claim 1 is directed to an assay for determining the concentration of rapamycin or a rapamycin analog in a sample, the rapamycin or rapamycin analog being capable of binding to FKBP12 protein or a binding domain thereof, the assay comprising: (i) contacting the sample with FKBP12 protein, or with a rapamycin binding fragment of the FKBP12 protein that maintains the rapamycin binding properties, for a time period and under conditions allowing formation of rapamycin/FKBP12 complex; (ii) contacting the rapamycin/FKBP12 complex with a complex-binding domain of mTOR for a time period and under conditions enabling binding of the complex to the complex-binding domain; (iii) detecting the amounts of said complex-binding domain that is bound to the rapamycin/FKBP12 complex; (iv) comparing the amounts detected in (iii) to a calibration curve, thereby determining the concentration of the rampamycin in the sample. Claims 2-4 and 7-9 and 13-17 depend, either directly or indirectly, from claim 1.

Claim 20 is directed to a kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample, the kit comprising: a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate; and a complex-binding domain of mTOR linked to a label that may be detected or that

may generate a signal. Claims 21-25 depend, either directly or indirectly, from claim 20.

In contrast to the presently claimed subject matter, MacFarlane et al. is directed to a method of assaying a sample of blood or blood components for the concentration of an immunophilin ligand. The method described in MacFarlane includes: incubating the sample with a nonionic detergent and a protease; inactivating the protease, and determining the concentration of the immunophilin ligand in the sample. *See* MacFarlane et al. at the Abstract. Additionally, MacFarlane et al. describes the ability to free an immunophilin ligand from its binding protein for the purpose of assaying the concentration of the ligand. As MacFarlen et al. indicate, the assaying may be "...by any one of a number of methods known to those of ordinary skill in the art. Preferably, an immunoassay or receptor binding assay is used." *See* MacFarlane et al, column 4, lines 32-35.

However, unlike the presently claimed subject matter, Applicant submits that MacFarlane et al. do not teach or suggest ***an assay for determining the concentration of rapamycin or a rapamycin analog in a sample, the rapamycin or rapamycin analog being capable of binding to FKBP12 protein or a binding domain thereof***, the assay comprising: (i) ***contacting the sample with FKBP12 protein, or with a rapamycin binding fragment of the FKBP12 protein that maintains the rapamycin binding properties, for a time period and under conditions allowing formation of rapamycin/FKBP12 complex***; (ii) contacting the rapamycin/FKBP12 complex with a complex-binding domain of mTOR for a time period and under conditions enabling binding of the complex to

the complex-binding domain; (iii) detecting the amounts of said complex-binding domain that is bound to the rapamycin/FKBP12 complex; (iv) comparing the amounts detected in (iii) to a calibration curve, thereby determining the concentration of the rampamycin in the sample, as recited in claim 1. Additionally, Applicant submits that MacFarlane et al. do not teach or suggest ***a kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample***, the kit comprising: ***a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate***; and ***a complex-binding domain of mTOR linked to a label that may be detected or that may generate a signal***, as recited in claim 20. Additionally, Applicant notes that MacFarlane et al. do not teach or suggest an assay for determining a drug concentration in the blood circulation.

In contrast, MacFarlane et al. describe a process for ***releasing a drug, i.e., a bound immunophilin ligand*** from within the cells to make it possible to ***determine of the concentration of the bound ligand***. In this regard, according to MacFarlane et al., it is the concentration of the drug which is bound to immunophilin in the cell membrane which is assayed and ***not*** the concentration of the drug that is not in bound to the immunophilin, and in the blood circulation, as presently claimes. As such, the process of MacFarlane et al. does not need to be associated with one or more assaying procedure, and may utilize one or more of any known assays. T he process according to MacFarlane et al. is focused on how to release the bound immunophilin ligand, i.e., the bound drug, from the immunophilin with which it is associated, ***and not with one specific innovative assay.***

In order to release the bound drug from its association with the immunophilin, the process of MacFarlane et al. ***requires*** incubating the sample with a nonionic detergent and a protease to lyse cellular membranes and degrade the immunophilin, to thereby release the immunophilin ligand for assaying. *See* MacFarlane et al. at column 2, lines 50-54 and 64- 66. Accordingly, ***the process described in MacFarlane et al. requires sample pre-treatment***.

However, unlike MacFarlane et al., the presently claimed subject matter is directed to a specific assay for determining rapamycin or rapamycin analog concentration in a sample, which may be a body fluid, e.g., blood. In this regard, Applicant notes that one purpose of the present assay is to determine the concentration of rapamycin or an analog thereof, which is ***capable of binding to FKBP12 protein or a binding domain thereof***, namely that which may induce toxicity or that which concentration should be adjusted in order to avoid, e.g., graft rejection.

Applicant notes that, unlike MacFarlane et al., the sample does not need to be pretreated. Additionally, assaying is of rapamycin (or an analog thereof) which is capable of binding to FKBP12 protein and which exists in a sample and which concentration is assayed.

Furthermore, Applicant submits that ***the assay according to the presently claimed subject matter is directed to rapamycin that is not in association with an immunophilin and, therefore, capable of binding to an***

FKBP12 protein, which is present in the sample. In contrast, Applicant submits that MacFarlane et al. merely result in a ***protein-bound ligand*** that is freed from the protein only for the purpose of assaying and ***not of a free ligand, e.g., rapamycin, in a sample***. Applicant submits that rapamycin that is already bound to a protien or a fragment thereof, will not form a complex with the protein; therefore, will not be quantified under the assay conditions. In this regard, Applicant notes that procedure described in MacFarlane et al. may result in rapamycin that is already bound to a protien or a fragment thereof may be the result of incomplete lysing of cellular material.

Chen et al. do not remedy the deficiencies of Macfarlane et al. Chen et al. is directed to immunoassays performed with two different ligands tagged, which are immunologically bound together. *See* Chen et al. at the Abstract.

However, like MacFarlane et al., Chen et al. also do not teach or suggest ***an assay for determining the concentration of rapamycin or a rapamycin analog in a sample, the rapamycin or rapamycin analog being capable of binding to FKBP12 protein or a binding domain thereof***, the assay comprising: (i) ***contacting the sample with FKBP12 protein, or with a rapamycin binding fragment of the FKBP12 protein that maintains the rapamycin binding properties, for a time period and under conditions allowing formation of rapamycin/FKBP12 complex***; (ii) contacting the rapamycin/FKBP12 complex with a complex-binding domain of mTOR for a time period and under conditions enabling binding of the complex to the complex-binding domain; (iii) detecting the amounts of said complex-binding domain that

is bound to the rapamycin/FKBP12 complex; (iv) comparing the amounts detected in (iii) to a calibration curve, thereby determining the concentration of the rampamycin in the sample, as recited in claim 1. Additionally, Applicant submits that MacFarlane et al. do not teach or suggest ***a kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample***, the kit comprising: ***a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate***; and ***a complex-binding domain of mTOR linked to a label that may be detected or that may generate a signal***, as recited in claim 20. Accordingly, whether taken alone or together, neither Macfarlane et al. nor Chen et al. teach or suggest each and every element of the presently pending claims.

Applicant respectfully notes submits that Chen et al. describe the ability to assay the presence of a ligand in one of three techniques which are summarized in the background of Chen et al. *See* Chen et al at the column 2, lines 10-22, and throughout the background. One of the techniques, referred to therein as "the Sandwich technique," includes contacting a receptor ligand with an assay ligand to form a complex, which is then contacted with a test ligand. According to Chen et al., the immunoassays are not free of inaccuracies. For example according to Chen et al.:

> The various immunoassay techniques referred to above suffered from a variety of inaccuracies which result from inaccuracies in the amount of the receptor ligand which is present at any particular stage of operations. For instance, in the fluoro immunoassay techniques performed on the surface of an applicator, inaccuracies may occur in final test results where there

> are variations in the amount of the receptor ligand which is Originally bound to the test surface. Similarly, inaccuracies can occur where some quantity of the receptor ligand is lost from the test surface during the course of shipment or the immunoassay procedure itself.

In other words, Applicant submits that the immunoassays can Chen et al. cannot be regarded as being "...the most sensitive assays for detecting target analytes in the sample...," as the erroneously asserted by Examiner on page 8 of the Official Action. In fact, Applicant submits the aforementioned passage ***teaches away*** from the presently claimed subject matter, as well as the other cited references because.

Additionally, Applicant submits that there would be no motivation to modify Chen et al. to arrive at the presently claimed subject matter because modifying the Sandwich assay described in Chen et al. would result in an antibody that may recognize metabolites of rapamycin, and at the same time may not recognize analogs thereof, making such an assay less or practically unsuitable for the purposes of the invention.

Clakson et al. do not remedy the deficiencies of MacFarlane et al. and Chen et al. Clakson et al. is directed to materials and methods are for the regulation of biological events, such as, target gene transcription and growth, proliferation or differentiation of engineered cells. *See* Clakson et al. at the Abstract.

However, like Macfarlane et al. and Chen et al., Clakson et al. also do not teach or suggest ***an assay for determining the concentration of rapamycin or a rapamycin analog in a sample, the rapamycin or rapamycin analog being***

capable of binding to FKBP12 protein or a binding domain thereof, the assay comprising: (i) ***contacting the sample with FKBP12 protein, or with a rapamycin binding fragment of the FKBP12 protein that maintains the rapamycin binding properties, for a time period and under conditions allowing formation of rapamycin/FKBP12 complex***; (ii) contacting the rapamycin/FKBP12 complex with a complex-binding domain of mTOR for a time period and under conditions enabling binding of the complex to the complex-binding domain; (iii) detecting the amounts of said complex-binding domain that is bound to the rapamycin/FKBP12 complex; (iv) comparing the amounts detected in (iii) to a calibration curve, thereby determining the concentration of the rampamycin in the sample, as recited in claim 1. Additionally, Applicant submits that MacFarlane et al. do not teach or suggest ***a kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample***, the kit comprising: ***a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate***; and ***a complex-binding domain of mTOR linked to a label that may be detected or that may generate a signal***, as recited in claim 20. Accordingly, whether taken alone or together, none of MacFarlane et al., Chen et al. and Clakson et al. teach or suggest each and every element of the presently pending claims.

In further support of the patentability of the present subject matter, Applicant politely directs the Examiner's attention to US Patent No. 6,635,745 (the '745 patent), filed on the same year the Clackson et al. patent was granted and the later divisional application thereof (US Patent Application No.

2002/0002273), both to Sedrani et al. and assigned to Novartis, disclose a rapamycin assay. According to the '745 patent at paragraphs [0002] and [0003]:

> The lack of a sensitive and reliable assay which can be performed quickly and easily in a clinical setting has been a major obstacle to the development of rapamycin as a pharmaceutical...Previous efforts to develop assay kits for clinical monitoring have not been particularly successful.

Applicant submits that the aforementioned statement made by a leading company, i.e., Novartis, at a date later than the date of the invention by Clackson et al. provides an indication that the combination of the references cited by the Examiner to constitute a departure from the state of the art prior to the filing date of the present application. Therefore, Applicant submits that the presently claimed subject matter is not at all obvious because the state of the art after the date of invention was not sufficient for even a large drug company, such as, Novartis to develop such an assay.

Accordingly, Applicant submits that none of the cited references render the presently claimed subject matter obvious, within the meaning of either of 35 USC § 103(a) Thus, the Examiner is respectfully requested to withdraw this rejection of claims 1-4, 7-9, 13-17 and 20-25.

IV. At page 9 of the Official Action, claims 10, 12, 18, 19 and 26 have been rejected under 35 USC § 103(a) as obvious over MacFarlane et al. (US Patent No. 5,650,288) in view of Chen et al. (US Patent No. 4,385,126) and Clakson et al. (US Patent No. 6,187,757) in further view of Hammock et al. (US Patent No. 5,459,040).

The Examiner asserts that it would have allegedly been obvious to use a 96 well microtiter plate, wherein HRP is used as and enzyme label with 3,3',5,5'-tetramethylbenzidine as a substrate as taught by Hammock et al. in the method and kit of MacFarlane et al. in view of Chen et al. and Clakson et al.

In view of the remarks set forth herein, this rejection is respectfully traversed because a prima facie case of obviousness has not been established.

A brief outline of the relevant authority is set forth above. The discussion of 35 USC § 103 is incorporated herein by reference.

Independent claims 1 and 20 are discussed in detail above. The discussion of independent claims 1 and 20 is incorporated herein by reference. Claims 10, 12, 18 and 19 depend, either directly or indirectly, from claim 1. Claim 26 depends, either directly or indirectly, from claim 20.

Each of MacFarlane et al., Chen et al. and Clackson et al. are discussed in detail above. The discussion of each of MacFarlane et al., Chen et al. and Clackson et al. is incorporated herein by reference. As discussed, in contrast to the presently claimed subject matter, whether taken alone or in combination, none of MacFarlane et al., Chen et al. and Clackson et al teach or suggest ***an assay for determining the concentration of rapamycin or a rapamycin analog in a sample, the rapamycin or rapamycin analog being capable of binding to FKBP12 protein or a binding domain thereof***, the assay

comprising: (i) ***contacting the sample with FKBP12 protein, or with a rapamycin binding fragment of the FKBP12 protein that maintains the rapamycin binding properties, for a time period and under conditions allowing formation of rapamycin/FKBP12 complex***; (ii) contacting the rapamycin/FKBP12 complex with a complex-binding domain of mTOR for a time period and under conditions enabling binding of the complex to the complex-binding domain; (iii) detecting the amounts of said complex-binding domain that is bound to the rapamycin/FKBP12 complex; (iv) comparing the amounts detected in (iii) to a calibration curve, thereby determining the concentration of the rampamycin in the sample, as recited in claim 1. Additionally, Applicant submits that MacFarlane et al. do not teach or suggest ***a kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample***, the kit comprising: ***a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate***; and ***a complex-binding domain of mTOR linked to a label that may be detected or that may generate a signal***, as recited in claim 20.

Hammock et al. do not remedy the defecienceies of MacFarlane et al., Chen et al. and Clackson et al. Hammock et al. is directed to methods of assaying for the presence of, or amount of, a metal ion in a sample suspected of containing such ions. *See* Hammock et al. at the Abstract.

However, like MacFarlane et al., Chen et al. and Clackson et al., Hammock et al. also do not teach or suggest ***an assay for determining the concentration of rapamycin or a rapamycin analog in a sample, the***

rapamycin or rapamycin analog being capable of binding to FKBP12 protein or a binding domain thereof, the assay comprising: (i) ***contacting the sample with FKBP12 protein, or with a rapamycin binding fragment of the FKBP12 protein that maintains the rapamycin binding properties, for a time period and under conditions allowing formation of rapamycin/FKBP12 complex***; (ii) contacting the rapamycin/FKBP12 complex with a complex-binding domain of mTOR for a time period and under conditions enabling binding of the complex to the complex-binding domain; (iii) detecting the amounts of said complex-binding domain that is bound to the rapamycin/FKBP12 complex; (iv) comparing the amounts detected in (iii) to a calibration curve, thereby determining the concentration of the rampamycin in the sample, as recited in claim 1. Additionally, Applicant submits that MacFarlane et al. do not teach or suggest ***a kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample***, the kit comprising: ***a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate***; and ***a complex-binding domain of mTOR linked to a label that may be detected or that may generate a signal***, as recited in claim 20.

Accordingly, Applicant submits that none of the cited references render the presently claimed subject matter obvious, within the meaning of either of 35 USC § 103(a) Thus, the Examiner is respectfully requested to withdraw this rejection of claims 10, 12, 18, 19 and 26.

V. At page 10 of the Official Action, claims 10-12 have been rejected under 35 USC § 103(a) as obvious over MacFarlane et al. (US Patent No. 5,650,288) in view of Chen et al. (US Patent No. 4,385,126) and Clakson et al. (US Patent No. 6,187,757) in further view of Coligan et al. (of record).

The Examiner asserts that it would have allegedly been obvious to use a 96 well microtiter plate, Coligan et al. in the method and kit of MacFarlane et al. in view of Chen et al. and Clakson et al.

In view of the remarks set forth herein, this rejection is respectfully traversed because a prima facie case of obviousness has not been established.

A brief outline of the relevant authority is set forth above. The discussion of 35 USC § 103 is incorporated herein by reference.

Independent claim 1 is discussed in detail above. The discussion of independent claim 1 is incorporated herein by reference. Claims 10-12 depend, either directly or indirectly, from claim 1.

Each of MacFarlane et al., Chen et al. and Clackson et al. are discussed in detail above. The discussion of each of MacFarlane et al., Chen et al. and Clackson et al. is incorporated herein by reference. As discussed, in contrast to the presently claimed subject matter, whether taken alone or in combination, none of MacFarlane et al., Chen et al. and Clackson et al teach or suggest ***an assay for determining the concentration of rapamycin or a rapamycin analog in a sample, the rapamycin or rapamycin analog being capable of binding to FKBP12 protein or a binding domain thereof***, the assay comprising: (i) ***contacting the sample with FKBP12 protein, or with a rapamycin binding fragment of the FKBP12 protein that maintains the***

rapamycin binding properties, for a time period and under conditions allowing formation of rapamycin/FKBP12 complex; (ii) contacting the rapamycin/FKBP12 complex with a complex-binding domain of mTOR for a time period and under conditions enabling binding of the complex to the complex-binding domain; (iii) detecting the amounts of said complex-binding domain that is bound to the rapamycin/FKBP12 complex; (iv) comparing the amounts detected in (iii) to a calibration curve, thereby determining the concentration of the rampamycin in the sample, as recited in claim 1. Additionally, Applicant submits that MacFarlane et al. do not teach or suggest ***a kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample***, the kit comprising: ***a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate***; and ***a complex-binding domain of mTOR linked to a label that may be detected or that may generate a signal***, as recited in claim 20.

Coligan et al. do not remedy the deficiencies of MacFarlane et al., Chen et al. and Clackson et al. Coligan et al. is generally directed assays for antibody production. *See* Coligan et al. at section 1.

However, like MacFarlane et al., Chen et al. and Clackson et al., Coligan et al. also do not teach or suggest ***an assay for determining the concentration of rapamycin or a rapamycin analog in a sample, the rapamycin or rapamycin analog being capable of binding to FKBP12 protein or a binding domain thereof***, the assay comprising: (i) ***contacting the sample with FKBP12 protein, or with a rapamycin binding fragment of the FKBP12***

protein that maintains the rapamycin binding properties, for a time period and under conditions allowing formation of rapamycin/FKBP12 complex; (ii) contacting the rapamycin/FKBP12 complex with a complex-binding domain of mTOR for a time period and under conditions enabling binding of the complex to the complex-binding domain; (iii) detecting the amounts of said complex-binding domain that is bound to the rapamycin/FKBP12 complex; (iv) comparing the amounts detected in (iii) to a calibration curve, thereby determining the concentration of the rampamycin in the sample, as recited in claim 1.

Accordingly, Applicant submits that none of the cited references render the presently claimed subject matter obvious, within the meaning of either of 35 USC § 103(a) Thus, the Examiner is respectfully requested to withdraw this rejection of claims 10-12.

VI. At page 12 of the Official Action, claim 31 has been rejected under 35 USC § 103(a) as obvious over MacFarlane et al. (US Patent No. 5,650,288) in view of Chen et al. (US Patent No. 4,385,126) and Clakson et al. (US Patent No. 6,187,757) in further view of Abuknesha et al. (US Patent No. 5,723,304).

The Examiner asserts that claim 31 would be rendered obvious by the combination of MacFarlane et al., Chen et al., Clakson et al. and Abuknesha et al.

In view of the remarks set forth herein, this rejection is respectfully traversed because a prima facie case of obviousness has not been established.

A brief outline of the relevant authority is set forth above. The discussion of 35 USC § 103 is incorporated herein by reference.

Independent claim 20 is discussed in detail above. The discussion of independent claim 20 is incorporated herein by reference. Claim 31 depends indirectly from claim 20.

Each of MacFarlane et al., Chen et al. and Clackson et al. are discussed in detail above. The discussion of each of MacFarlane et al., Chen et al. and Clackson et al. is incorporated herein by reference. As discussed, in contrast to the presently claimed subject matter, whether taken alone or in combination, none of MacFarlane et al., Chen et al. and Clackson et al teach or suggest ***a kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample***, the kit comprising: ***a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate***; and ***a complex-binding domain of mTOR linked to a label that may be detected or that may generate a signal***, as recited in claim 20.

Abuknesha et al. do not remedy the defecienceies of MacFarlane et al., Chen et al. and Clackson et al. Abuknesha et al. is directed to a method of immunological detection, i.e., an immunoassy, a sensor and a test-kit. *See* Abuknesha et al. at the Abstract.

However, like MacFarlane et al., Chen et al. and Clackson et al., Abuknesha et al. also do not teach or suggest ***a kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample***, the kit comprising: ***a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate***; and ***a complex-binding domain of mTOR***

linked to a label that may be detected or that may generate a signal, as recited in claim 20.

Accordingly, Applicant submits that none of the cited references render the presently claimed subject matter obvious, within the meaning of either of 35 USC § 103(a) Thus, the Examiner is respectfully requested to withdraw this rejection of claim 31.

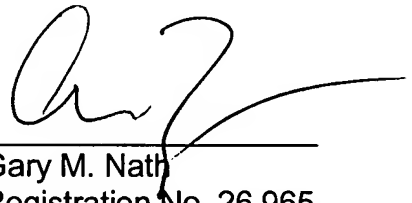
CONCLUSION

Having made the required election, examination on the merits is earnestly solicited. Should the Examiner deem that any further action by Applicant's undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

In the event this paper is not timely filed, Applicant petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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